I. INTRODUCTION

A. Overview of the ETS Home Visit Manual of Operations

As a Home Visitor for the study titled Project DC-STEP: Prevention of Environmental Tobacco Smoke Exposure (ETS) during the First Year of Life (also known as the Healthy Infants and Mothers Program), you will be responsible for visiting the homes of study participants to conduct assessment activities designed to evaluate the ETS intervention program and the safety and development attention-control intervention. The purpose of the Home Visit Manual of Operations is to provide documentation necessary for orientation, training, and implementation of home visiting activities. Recruiting and screening to identify potentially eligible participants, conducting the telephone interview assessments, and delivering the intervention program are tasks assigned to other study personnel and thus, procedures for conducting these activities are included in separate Manuals of Operations.

Revisions and additions to all Manuals will be distributed to study personnel as dated replacement pages to be inserted in the existing Manuals. These revisions/additions will ensure that all protocol requirements are documented and implemented. In addition, the Manuals of Operations will serve as a historical summary of the operations of this project.

B. NIH-DC Initiative:

1. Background and Study Rationale

In 1990, the infant mortality rate in the District of Columbia was 20 per 1000 live births, a rate higher than that of any of the 50 states and among the highest for any city with a population greater than 500,000. The infant mortality rate is expressed in terms of the number of infants who die in their first year of life per 1,000 live births. The infant mortality rate decreased from 29 per 1000 in 1970 to a low level of 18 per 1000 in 1983. The rate increased to 23 per 1000 in 1989. A major determinant of the high infant mortality in the District of Columbia is the high rate of low weight births. During this period the low birth weight (LBW) rate among African Americans increased from 13% to 17.6%.

In response to the need to reduce infant mortality in the District of Columbia and to eliminate the disparity in minority populations, the National Institute of Child Health and Human Development (NICHD), in conjunction with the National Institutes of Health Office of Research on Minority Health and the National Institute for Nursing Research, began a collaborative effort to develop coordinated projects designed to better understand the reasons for the high rate of infant mortality in the District of Columbia and to develop and evaluate intervention projects aimed at reducing the number of infants in the District who are at increased risk of dying in their first year of life. The project, entitled "*The NIH-DC Initiative to Reduce Infant Mortality among Minority Populations in Washington, DC*" (NIH-DCI) began in the fall of 1992 and was funded for five years.

The grantees in Phase I of the NIH-DCI included Children's National Medical Center (CNMC), the DC Commission of Public Health, DC General Hospital (DCGH), Georgetown

University (GU), Howard University (HU), and the University of the District of Columbia (UDC). The Greater Southeast and Providence Hospitals (affiliated with Georgetown University), the George Washington University (GWU) (affiliated with Children's Hospital), the DC Office on Latino Affairs, and the Department of Corrections (in partnership with the DC Commission of Public Health) were also in the program. RTI International was selected as the Data Coordinating Center (DCC) for the program in 1993.

The goal of Phase I was to better understand the reasons why some women may be at higher risk of having a LBW infant and why some infants are at increased risk of dying early in life. Populations studied included the following: inner-city pregnant or postpartum women and/or their children recruited through primary care facilities, public health clinics or inpatient settings; students in 7th grade in Washington DC middle schools; and infants up to age 36 months who were treated in hospital emergency rooms or admitted to hospitals with injuries. The following eight studies were approved and carried out during Phase I (ending April 30, 1998):

- Pride in Parenting: Parenting Education Impacts on Health Care Utilization
- The Association of Neonatal Outcomes with the Characteristics of Neonatal Units
- Lack of Age-Appropriate Immunizations Among Infants and Young Children Born in the District of Columbia
- Preventing Adolescent Pregnancy
- The Prevention of Fetal Alcohol Effects in the District of Columbia
- Barriers, Motivators, and Facilitators of Prenatal Care Utilization in Washington, D.C.: A Program of Research
- The Prevention of Childhood Injuries
- Evaluation of Health Systems for Pregnant Medicaid Recipients in the District of Columbia.

Phase II of the program was funded starting on May 1, 1998 and ended on April 30, 2004, with four grantees: CNMC, GU, GWU, and HU. RTI International was also selected as the DCC for this phase. In this phase, the results of the Phase I studies are being combined with other information to develop and test strategies to lower risks for adverse pregnancy outcomes. The following three studies were approved and carried out during the period:

- Adolescent Pregnancy Prevention Phase II (also called "Building Futures for Youth")
- Interventions For Risk Factors In Pregnant Women In Washington, D.C.: An Integrated Approach (also called "Project DC-HOPE" [Healthy Outcomes of Pregnancy Education])
- Fetal Alcohol, Phase II (also called "Alcohol Assessment Project")

A third 5-year phase of the program was funded starting on May 1, 2004 with the same four grantees from Phase 2: CNMC, GU, GWU, and HU. Again, RTI International was also selected as the DCC for this phase. The following five studies were approved and will be carried out during this Phase III period:

- Prevention of Environmental Tobacco Smoke (ETS) Exposure in Children Age 0-12 Months (also referred to as the DC-STEP: Healthy Infants and Mothers Program)

- The Efficacy of Nicotine Replacement Therapy to Reduce the Risk of Nicotine Exposure in Pregnant Minority Smokers (also referred to as the DC-STEP: NRT Study)
- Adolescent Pregnancy Prevention Phase III (also called "Building Futures for Youth")
- Building Healthy Teen Relationships and Reproductive Practices to Increase Inter-pregnancy intervals. (also called "Girl Talk for Teen Moms")
- Pharmacokinetics of Nicotine and Cotinine in Pregnant African-American Women and Implications for Pharmacological Interventions, Part A.

As indicated above, the purpose of this manual is to focus on home visit procedures for the ETS Study. The ETS Study is one of two study protocols being conducted as part of Project DC-STEP.

2. Administration

The major organizational components for the Phase III NIH DCI studies include the NIH-DC Initiative Cooperative Agreement Grantee Organizations: Children's National Medical Center (PI: Larry D'Angelo, M.D.), Georgetown University Medical Center (PI: K.N. Siva Subramanian, M.D.), George Washington University Medical Center (PI: Ayman A.E. El-Mohandes, M.D., M.P.H.), Howard University (PI: Renee Jenkins, MD); the DCC (RTI International, PI: Nabil El-Khorazaty, Ph.D.); and the NICHD Program Office (Program Officer, Michele Kiely, Dr.Ph.).

The Phase III NIH-DCI Executive Steering Committee, comprised of the four PIs of the Primary Grantee sites, the DCC, and the NICHD representative, provides the scientific direction for all studies.

C. Project DC-STEP: Study Organization and Monitoring

As indicated above, Project DC-STEP consists of two study protocols (the NRT and ETS Studies) being conducted as part of Phase III of the NIH-DCI. Both studies have been developed as part of a coordinated effort among investigators from the following Phase III NIH-DCI grantee sites: GWU, CNMC, and GU.

In addition to the grantee sites, Project DC-STEP includes investigators from RTI International, which serves as the DCC and provides assistance with development of measures, data monitoring and study implementation of protocols and procedures, and the NICHD, which is the funding institution and collaborates by providing scientific oversight to the study. All recruitment, intervention and evaluation staff and research team members will receive training and oversight from the PI, Co-PI, Co-Investigators and the collaborating institutions. The names of the study investigators and the role of each participating institution for the ETS Study (i.e., the study for which you will be conducting the home visits) is provided in ***Section I.D*** below.

During Phases I and II of the NIH-DC Initiative, comprehensive guidelines were developed to ensure data accuracy, confidentiality and adverse event reporting. During Phase III, similar procedures will be developed for the proposed protocols in coordination with the NIH

Scientific Coordinator (Project Officer) and the DCC. For example, recruitment staff will be trained to ascertain and confirm eligibility prior to recruitment. Recruitment specialists, home visitors, and intervention staff will maintain a heightened awareness for any potential risks that could be attributable to study participation. Any adverse events identified will be reported to the Project Data and Safety Monitoring Board (DSMB) of the study who will in turn determine the need to report these events further to the Institutional Review Boards (IRBs) of each participating institution and the NICHD. Mechanisms will be instituted to deal with any adverse events that may represent a health hazard to a pregnant mother or to the infant. Reporting of such instances to the health care providers for further action will occur when needed.

The DSMB will be responsible for periodic review of the study results and the Cumulative Adverse Event Report. Based on these periodic reviews, the DSMB will determine the safety of the study and whether the randomized intervention has reached, or is likely to reach, significance for the desired outcome in the intervention group. The DSMB in consultation with the Program Scientific Coordinator will determine the adequacy of the plan for safety reporting according to the study protocol and the appropriate frequency of their periodic deliberations.

D. Project DC-STEP: ETS Study Overview

Two interrelated research efforts are being conducted as part of the ETS Study: 1) a randomized behavioral intervention trial to reduce ETS exposure of children age 0-12 months using a repeated measures design, and 2) a prospective cohort study to assess the number and types of health effects, major and minor, associated with prenatal and postpartum exposure to tobacco smoke products (TSP) and ETS among infants during the first year of life.

1. DC-STEP: ETS Study Organization

As the Principal Investigator (PI), Susan Blake, Ph.D. (GWU) provides direct oversight for the development, implementation and analysis of the ETS study. She works closely with the Co-PI, Dana Best. M.D., M.P.H. (CNMC) who oversees work related to health outcomes component of the study (described in ***Section D.2*** below). Other co-investigators from GWU providing technical and substantive input include: Ayman El-Mohandes, M.D., M.P.H. and Richard Windsor, MS, PhD, MPH. Investigators from GWU are also responsible for hiring and supervising the recruitment and intervention staff (i.e., the Recruitment Specialists who will also serve as the Infant Health Advisors) and medical record abstractors.

Additionally, Kathy Katz, Ph.D. from Georgetown University provides oversight for the implementation of the attention-control group (i.e., the safety and development intervention described below) and hiring of the home visitor to conduct home visit assessments, and Mary Ann Rossi, Ph.D., from Children's Hospital oversees the conduct of the telephone interviews and supervises the interviewing data collection staff.

Other investigators include, Michele Kiely, Ph.D., the NICHD PI who oversees scientific activities on behalf of the funding agency, and Nabil El- El-Khorazaty, Ph.D. and Jutta Thornberry from RTI who oversee data coordinating center activities.

Dr. Hovell, from San Diego State University, who has conducted numerous ETS measurement and intervention studies to prevent ETS exposure during childhood, also serves as a consultant investigator to this study.

2. Primary and Secondary Objectives

The primary objective of the ETS study is to test the efficacy of a brief, clinic-based intervention to prevent ETS exposure during infancy that is consistent with clinical practice guidelines. The study is a randomized behavioral intervention trial to reduce ETS exposure of children age 0-12 months using a randomized repeated measures design.

The secondary objective is to assess the frequency and types of health effects, major and minor, associated with prenatal and postpartum exposure to TSP and ETS among infants. This is a prospective cohort study to assess the number and types of health effects, major and minor, associated with prenatal and postpartum exposure to TSP and ETS among infants in the first year of life.

3. Study Design

A two-group, repeated measures random assignment design will address the primary aim of the ETS study to test the efficacy of an intervention designed to prevent ETS exposure during the first year of life. Women will be classified into three cohorts based on self-reported cigarette smoking and ETS exposure and saliva cotinine validated levels, and then randomized by strata to the experimental (i.e.,. the ETS intervention) and control (i.e., the safety and development attention-control intervention) groups. Random assignment to the experimental and control groups will be stratified by cohort. The first qualified participant within each stratum of women in each cohort will be randomized to the intervention or control groups to assure an equal number of mother-child dyads in each strata.

Pregnant Black, African American and Hispanic women who are living in the Washington, D.C. metro area who are at least 18 years of age will be recruited through prenatal care clinics between 28-35 weeks of gestation. A list of all eligibility criteria for study participation is included in ***Exhibit I-1***. Based upon self-reported and salivary cotinine-verified levels of maternal smoking and ETS exposure during pregnancy, recruited mothers will be classified into one of the following three cohorts: (1) women who continue to smoke during pregnancy (who report that they smoked in the past 7 days), or whose salivary cotinine at the time of recruitment is $\geq$18ng/ml (Cohort 1: n=125); (2) women who report quitting or having reduced smoking during pregnancy, and whose salivary cotinine at the time of recruitment is $\leq$17ng/ml (Cohort 2:n=125); and (3) women who did not smoke before or during their pregnancy, but who report household ETS exposure during pregnancy, or whose partners or household members smoke, and whose salivary cotinine at the time of recruitment is $\geq$5 ng/ml and $\leq$17ng/ml (Cohort 3: n=125). Women will continue to be enrolled into the study until the specified sample sizes for each of these three groups is met.

Exhibit I-1: Project DC-STEP: ETS Study Eligibility Criteria

To be eligible for the **ETS Study**, a woman must also:

- at least 18 years of age;
- reside in the District of Columbia or Greater Metropolitan Area;
- self-identify as Black, African American or Hispanic;
- have a normal, singleton pregnancy, and
- able to read and speak English.
- be between 28-35 weeks pregnant, and
- initiate prenatal care prior to 28 weeks gestation,

Women will be *excluded* or *terminated* early from the ETS study if any of the following apply either at enrollment or occur during the course of the study:

- Report suicidal intentions, have a major psychiatric illness, or are in withdrawal from addictive substances requiring hospitalization or methadone treatment;
- Are currently incarcerated;
- Experience delivery complications requiring maternal hospital stay of 7 days or more;
- Give birth to a child who is born at less than 34 weeks gestation, weighs less than 1800 grams at birth, or requires neonatal intensive care unit (NICU) treatment for more than 12 hours; or
- Report losing custody of the child during the study period.

It is anticipated that the above stratified sampling design will control for varying levels of prenatal cigarette smoking and ETS exposure, and depending on levels of postpartum smoking and exposure, enable an exploratory analyses of the differential impact varying levels of prenatal and postpartum exposure may have on infant health outcomes in the first year of life.

4. Sample Size and Participating Hospitals

A total of 375 pregnant Black, African American, and Hispanic women will be recruited from three prenatal care clinics in Washington, D.C. (i.e., George Washington University Obstetric Clinic, Providence Hospital Obstetric Clinic, and Chartered Health Center). As discussed above, they will be classified into three cohorts based on their self-reported and salivary cotinine-verified levels of maternal smoking and ETS exposure during pregnancy. Study enrollment will continue until the specified sample sizes for each of these three groups is met. Women will be randomized into the experimental and control groups; randomization will be stratified by cohort and recruitment site.

5. Variables of Interest and Their Measurement

a. Measures

A number of measures will be used on the ETS Study to determine whether the study objectives have been met. These measures consist of biospecimen samples to determine

maternal and infant cotinine levels (i.e., we will collect maternal saliva and urine and infant urine), telephone interviews, and home visit assessments.

At recruitment, maternal salivary and urinary cotinine assessments will be conducted to verify self-reports and to determine cohort status.

Maternal telephone interviews will be conducted at baseline (within 1 month of enrollment), at 6-weeks postpartum, and at 4-, 6-, and 12-months postpartum. Telephone interviews are designed to collect the following types of information: demographic background, pregnancy and family medical history, tobacco use and exposure to other people's cigarette smoke during pregnancy, strategies to reduce tobacco use and exposure, stressful life events, drug and alcohol use in pregnancy, and sources of social support. Postpartum telephone interviews will also include questions about tobacco use and maternal and infant exposure to other people's cigarette smoke after pregnancy; breastfeeding; parenting practices; and infant behavior, temperament, growth, safety and health.

In addition to the telephone interviews, a Home Visitor will also visit each woman's home at baseline, 6-weeks postpartum, and 6- and 12-months postpartum. Each home visit assessment consists of two home visits which are scheduled one week apart. During the *first home visit for the baseline assessment*, the Home Visitor (1) draws a map of the household structure (for placement of nicotine monitors and safety observation) and collects data regarding household composition; (2) places an active household ambient nicotine monitor in the home (several other monitors will also be left in the home); (3) conducts a home safety observation assessment (i.e., the Home Accident Prevention Inventory); and (4) and asks the mother to complete Tymchuk's Inventory of Home Dangers and Safety Precautions. These activities are also completed during the first home visit for each post-partum home visit assessment (i.e., when the infant is 6-weeks, and 6- and 12-months old). Additionally, *during the first home visit for each postpartum home visit assessmen*t, the home visitor will distribute and explain how to complete the 7-Day Activity Diary which will be used to assess the infant's exposure to ETS and TSP during the past seven days.

For each home visit assessment, the Home Visitor returns to the home one week later for a second home visit. *During the second home visit for the baseline assessment*, the Home Visitor will (1) collect the nicotine monitors; (2) collect the maternal saliva sample (for cotinine assessments); and (3) ask the mother to complete the self-administered Tobacco Smoke Exposure Questionnaire. *During the second visit for the postpartum home visits*, the home visitor *also* collects an infant urine sample and administers the smoking and ETS questions as part of the 7-Day Activity Diary.

b. Outcomes

Specific Aim # 1: ETS Intervention Study Outcomes. This aim calls for determining the effects of the intervention on infants' ETS exposure using data collected from women in all three cohorts. Since women in the ETS intervention group will be encouraged to prevent infant exposure to ETS and postpartum relapse, we hypothesize that infant urine cotinine levels and maternal reports of infant ETS exposure will increase more among the attention-control families compared to those in the ETS intervention group over time. Similarly, it is expected that household nicotine levels and maternal salivary cotinine levels will increase more among participants in the attention-control group compared to the ETS intervention group.

We will explore 1) dose-response effects between completion of intervention sessions and infant ETS exposure, 2) maternal relapse rates and smoking levels between groups, and 3) changes in mediating/moderating factors targeted in the ETS intervention group (e.g., partner or other household member smoking levels, breastfeeding, maternal smoking relapse postpartum,) and prevention of infant ETS exposure. Since the attention-control group will receive a safety and development intervention, we will similarly explore those results as well. Assessments will include standardized and adapted measures reflecting parenting practices (e.g., supervision, routines, protectiveness), home safety knowledge and practices, parent-child interactions at 6-weeks, 4-, 6-, and 12-months, and child social-emotional competence (at 12-months only) using the Brief Infant-Toddler Social and Emotional Assessment (BITSEA).

Exploratory Aim # 2: Infant Health Study Outcomes. As part of our analyses for Exploratory Aim # 2, we will assess infant negative health outcomes associated with levels of TSP/ETS exposures during pregnancy and postpartum. We recognize that it is not the acute level of TSP/ETS exposure that may be a critical determinant of child health outcomes, but cumulative ETS exposure levels over years. This study will not be able to address the issue of prolonged cumulative exposures since 1) we will not be assessing prenatal exposures throughout pregnancy, other than retrospectively, 2) we will not be measuring continuous infant ETS exposure postpartum as our measures are scheduled only four times during the first 12 months, 3) we are not enrolling a non-TSP/ETS exposure group, and our experimental groups will likely not have reduced infant ETS exposure to zero postpartum, and 4) short term follow-ups over the course of the first year of life are not likely to show strong health effects. However, this study will set the stage for future epidemiological studies to assess the health effects of cumulative levels of exposure over longer study intervals.

The intent of this secondary analysis is to estimate the relative risk for all possible ETS-related adverse health outcomes in children based upon ETS (passive exposure) postpartum, maternal smoking and/or ETS exposure during pregnancy (gestational exposure), or both.

We will use both maternal self-reports of prenatal and postpartum TSP/ETS exposure, as well as more precise measures of infant urine cotinine that can detect very small levels of ETS exposure postpartum. Infant urinary cotinine levels measured across the year will be used to stratify infants into ETS-exposed, and minimally or non-exposed groups of infants postpartum (using a cut-off of 10ng cotinine per mg of creatinine in infant urine). Retrospective maternal reports of cigarette smoking and ETS exposure during pregnancy, combined with confirmatory salivary cotinine levels at the baseline prenatal assessment (taken in the 3rd trimester), will enable stratification of infants who were prenatally exposed to TSP in utero at varying levels.